Indinavir

Brand Name: Crixivan
Drug Class: Protease Inhibitors

Drug Description

Indinavir sulfate, the salt form of the active drug indinavir, is a synthetic antiretroviral agent and a peptidomimetic protease inhibitor (PI). [1]

HIV/AIDS-Related Uses

Indinavir sulfate was approved by the FDA on March 13, 1996, for use in combination with other antiretroviral agents or as monotherapy for the treatment of HIV infection.[2] Evidence suggests that use of a three-drug regimen that includes indinavir and two nucleoside reverse transcriptase inhibitors (NRTIs) can increase CD4 cell counts and decrease plasma HIV-1 RNA levels in pediatric patients who previously received long-term therapy with nucleoside reverse transcriptase inhibitors, especially if the three-drug regimen includes NRTIs not used in previous regimens.[3]

Indinavir sulfate is also used in conjunction with other antiretroviral agents for postexposure prophylaxis of HIV infection in healthcare workers and others who have had occupational exposure to HIV.[4]

Pharmacology

Indinavir is a selective, competitive, reversible inhibitor of HIV protease, an enzyme that plays an essential role in HIV replication and the formation of infectious virus. Indinavir is a structural analogue of the HIV Phe-Pro protease cleavage site. The drug's structure inhibits the function of HIV protease, blocking virus maturation and causing the formation of immature, noninfectious virions. Indinavir is active in both acutely and chronically infected cells; chronically infected cells are not affected by nucleoside reverse transcriptase inhibitors (NRTIs). While indinavir does not affect early stages of the HIV replication cycle, it does interfere with the production of infectious HIV, limiting further infectious spread of the virus.[5] Indinavir is active against HIV-1 and HIV-2.[6]

Indinavir is rapidly absorbed from the gastrointestinal (GI) tract, with peak plasma concentrations of the drug generally occurring in less than 1 hour and averaging 0.8 hours in fasting adults. Presence of food in the GI tract can substantially decrease the extent of absorption of oral indinavir.[7]

Distribution of indinavir into body tissues and fluids has not been fully characterized. Indinavir has been detected in low concentrations in the cerebrospinal fluid of adults or children receiving the drug.[8]

Indinavir sulfate is in FDA Pregnancy Category C. Adequate and well-controlled studies have not been done in pregnant women. The optimal dosing regimen for pregnant patients has not been established. A dose of indinavir, 800 mg three times daily, with zidovudine and lamivudine has been studied in 16 HIV infected pregnant patients enrolled at 14 to 28 weeks gestation. The mean area under the concentration-time curve (AUC) at 30 to 32 weeks gestation was 74% lower than at 6 weeks postpartum. The mean trough plasma concentration (Cmin) in 55% of these patients was below assay threshold for quantification. Based on the substantially lower drug exposures and the limited data in HIV infected pregnant patients, indinavir use is not recommended.[9]

It is not known whether indinavir crosses the placenta in humans; it does cross the placenta in laboratory animals. Hyperbilirubinemia has occurred in patients receiving indinavir sulfate, but it is unknown whether drug administered during pregnancy will exacerbate hyperbilirubinemia in neonates.[10]

Indinavir sulfate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. An Antiretroviral Pregnancy Registry has been established to monitor the outcomes of pregnant women exposed to indinavir. Physicians may register patients by calling 1-800-258-4263 or online at http://www.APRegistry.com. Although it is not known whether indinavir is excreted in human milk, there exists the potential for adverse effects from indinavir in nursing infants. Mothers should be instructed to discontinue nursing if they are receiving indinavir.[11]

Indinavir

Pharmacology (cont.)

Protein binding of indinavir is moderate and approximately 60% over a range of 0.05 to 10 mcg/ml.[12]

The metabolic fate of indinavir has not been fully determined, but the drug is metabolized in the liver. Systemic clearance of indinavir is rapid; the plasma half-life of indinavir averages 1.8 hours in adults and 1.1 hours in children. Indinavir is metabolized to at least seven metabolites, including one glucuronide conjugate and six oxidative metabolites. In vitro studies indicate that cytochrome P (CYP) 3A4 is the major enzyme involved in the formation of the oxidative metabolites. Indinavir is excreted primarily in the feces both as unabsorbed drug and as metabolites. Following a 400 mg oral dose, 83% was recovered in feces (19.1% as unchanged drug) and 19% was recovered in urine (9.4% as unchanged drug). It is not known if indinavir is removed by hemodialysis or peritoneal dialysis.[13]

Although the complete mechanisms of resistance or reduced susceptibility to indinavir have not been fully determined to date, acquisition of multiple HIV protease mutations appears to be necessary for high-level resistance to the drug. In vitro studies indicate that the antiretroviral effects of indinavir and some NRTIs are additive or synergistic against HIV-1, and there is evidence from clinical studies that antiretroviral regimens that include indinavir and one or two nucleoside agents can suppress in vivo viral replication to a greater extent than monotherapy. There is also evidence that use of regimens that suppress HIV replication to levels that cannot be detected by sensitive plasma HIV-1 RNA assays is associated with a lower viral mutation rate and may delay or prevent the emergence of resistance. Several studies indicate that the incidence of HIV protease mutations and HIV reverse transcriptase mutations associated with indinavir or zidovudine resistance, respectively, is lower in isolates obtained from patients receiving indinavir/zidovudine combination therapy than in isolates obtained from patients receiving monotherapy with these drugs.[14]

Some degree of cross resistance can occur among the various PIs. Further study is needed to more fully evaluate the extent and clinical implications of cross-resistance among the drugs and to determine whether administration of one PI has any effect on subsequent therapy with any other PI.[15] Cross resistance between indinavir and reverse transcriptase inhibitors is thought to be unlikely because they affect different enzyme target sites; however, cross resistance was observed between indinavir and ritonavir, another PI. Varying degrees of resistance have been noted between indinavir and other PIs.[16] [17]

Adverse Events/Toxicity

Adverse effects commonly observed with indinavir use include nephrolithiasis/urolithiasis, jaundice, diabetes or hyperglycemia, ketoacidosis, asthenia, GI disturbances (abdominal or stomach pain, nausea, diarrhea, vomiting), headache, insomnia, taste perversion, acid regurgitation, anorexia, appetite increase, cough, dizziness, fever, rash, and somnolence.[18]

The most frequently clinically reported serious adverse effect of indinavir sulfate is nephrolithiasis/urolithiasis. This effect appears to be dose related, occurring more frequently in patients receiving more than 2.4 grams daily and is significantly more frequent in pediatric patients. If symptoms of nephrolithiasis/urolithiasis (flank pain with or without hematuria) occur, temporary interruption or discontinuation of indinavir sulfate therapy may be considered.[19] To ensure adequate hydration, which reduces the risk of developing nephrolithiasis, the manufacturer recommends that adults receiving indinavir sulfate drink at least 1.5 liters of water per day.[20]

Some patients receiving indinavir sulfate have developed acute hemolytic anemia, with some cases resulting in death. Hepatitis, including cases resulting in hepatic failure and death, has been reported in patients treated with indinavir, though a causal relationship between indinavir use and these events has not been established. Administration of PIs such as indinavir may cause new onset of diabetes mellitus or exacerbation of pre-existing diabetes mellitus and hyperglycemia, but a causal relationship has not been established between PI therapy and these events.[21]

Drug and Food Interactions

Presence of food in the GI tract substantially decreases absorption of indinavir. In clinical studies, administration with a meal high in calories, fat, and protein resulted in a 77% +/- 8% AUC reduction and an 84% +/- 7% reduction in peak plasma concentration. Administration with lighter meals resulted in little or no change in the indinavir AUC, peak plasma concentration, or trough concentration.[22] For optimum absorption, indinavir should be administered with water 1 hour before or 2 hours after a meal.[23]

Both indinavir and atazanavir are associated with indirect hyperbilirubinemia. Combinations of these drugs have not been adequately studied and coadministration of indinavir and atazanavir is not recommended.[24] Delavirdine inhibits the metabolism of indinavir such that coadministration of indinavir 400 mg or 600 mg three times daily with delavirdine 400 mg three times daily alters indinavir AUC, Cmax, and Cmin. Conversely, indinavir had no effect on delavirdine pharmacokinetics.[25] In a small, volunteer-based study, twice-daily coadministration of indinavir 800 mg with ritonavir with food for two weeks resulted in a 2.7-fold increase in daily indinavir AUC, 1.6-fold increase in indinavir Cmax, and an 11-fold increase in indinavir Cmin for a ritonavir 100 mg dose. With a ritonavir 200 mg dose, there was a 3.6-fold increase of daily indinavir AUC, a 1.8-fold increase in indinavir Cmax, and a 24-fold increase in indinavir Cmin. In the same study, twice-daily coadminstration of indinavir with ritonavir (100 or 200 mg) resulted in daily ritonavir AUC increases not observed in people who received the same doses of ritonavir alone.[26]

If both didanosine and indinavir are part of a treatment regimen, they should be administered at least 1 hour apart on an empty stomach. A normal acidic pH may be necessary for the optimal absorption of indinavir, and didanosine requires a buffer to increase the pH so that acid does not rapidly degrade didanosine in the stomach.[27]

Competition of CYP3A4 substrates by indinavir could inhibit the metabolism of astemizole, cispride, ergot derivatives, midazolam, pimozide, and triazolam, resulting in elevated plasma concentrations of these medications. Thus, concurrent administration with indinavir raises the potential for serious and/or life threatening side effects. Concurrent use of ketoconazole and indinavir results in a 68% increase in the AUC of indinavir; a dosage reduction of indinavir to 600 mg every 8 hours is recommended when these medications are coadministered.[28]

Concurrent use of rifabutin and indinavir results in a 32% increase in the AUC of indinavir and a 204% in the AUC of rifabutin. Dosage reduction of rifabutin to 400 mg every 8 hours is necessary when it is coadministered with indinavir. Because rifampin is a potent inducer of CYP3A4, which could significantly decrease the plasma concentration of indinavir, concurrent use with indinavir is not recommended.[29]

Concomitant use of indinavir with lovastatin or simvastatin is not recommended. Caution should be used when any PIs, including indinavir, are used concurrently with other HMG-CoA reductase inhibitors (atorvastatin or cerivastatin). The risk of myopathy or rhabdomyolysis may be increased when PIs are used with these drugs.[30] Concomitant use of indinavir and St. John's wort (Hypericum perforatum) or products containing St. John's wort may substantially decrease indinavir concentrations and may lead to loss of virologic response and possible resistance to indinavir or other PIs.[31]

Coadministration of indinavir and sildenafil, tadalafil, or vardenafil is expected to substantially increase sildenafil, tadalafil, or vardenafil plasma concentrations and the risk of phosphodiesterase type 5 (PDE) inhibitor-associated adverse effects, including hypotension, visual changes, and priapism. Patients receiving a PDE5 inhibitor should report any symptoms to their doctors.(11) Indinavir (800 mg every 8 hours) coadministered with a single 10 mg dose of vardenafil results in a 16-fold increase in vardenafil AUC, a sevenfold increase in vardenafil Cmax, and a twofold increase in vardenafil half-life.[32]

In vitro drug metabolism studies suggest that there is a potential for drug interactions when trazodone is given with CYP3A4 inhibitors. It is likely that indinavir, a CYP3A4 inhibitor, may lead to

Drug and Food Interactions (cont.)

substantial increases in trazodone plasma concentrations with the potential for adverse effects. If trazodone is used with a potent CYP3A4 inhibitor, a lower dose of trazodone should be considered.[33]

Coadministration of indinavir and efavirenz reduces indinavir levels. Clinical data suggest that when indinavir is used in combination with efavirenz, increasing the dosage of indinavir to 1000 mg once every 8 hours is not sufficient to compensate for this drug interaction. In a 10-day study investigating indinavir 1000 mg administered every 8 hours with efavirenz, the indinavir AUC decreased 33% to 46% and the Cmin decreased 39% to 57%. The addition of ritonavir 100 to 200 mg twice daily may help to boost concentrations of indinavir when coadministered with efavirenz, but data on the optimal dosage is not available.[34]

Contraindications

Indinavir sulfate is contraindicated in patients with clinically significant hypersensitivity to indinavir or any of its components.[35]

Clinical Trials

For information on clinical trials that involve Indinavir, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Indinavir AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[36]

Dosage Form: Capsules containing indinavir 100, 200, 333, and 400 mg.[37] [38]

The recommended dosage of indinavir is 800 mg (two 400 mg capsules) every 8 hours. In patients with mild to moderate hepatic insufficiency due to cirrhosis, the dose of indinavir should be reduced to 600 mg every 8 hours. The prescribing information provided by the manufacturer details specific dosing adjustments when indinavir is coadministered with delavirdine, didanosine, efavirenz, itraconazole, ketoconazole, and rifabutin.[39]

Storage: Store at room temperature, 15 C to 30 C (59 F to 86 F), in a tightly closed container. Indinavir sulfate capsules are sensitive to moisture and should be dispensed and stored in the original container with a desiccant. Store unit-dose packages at 15 C to 30 C (59 F to 86 F). Protect from moisture.[40]

Chemistry

CAS Name:

Indinavir

Chemistry (cont.)

CAS Number: 157810-81-6 (indinavir sulfate)[42]

150378-17-9 (indinavir)[43]

Molecular formula: C36-H47-N5-O4.H2-SO4[44]

C60.74%, H6.94%, N9.84%, O17.98%, S4.50%[45]

Molecular weight: 711.88[46]

Melting point: 150 to 153 C[47]

Physical Description: White to off-white, hygroscopic, crystalline powder.[48]

Solubility: Very soluble in water and in methanol.[49]

Other Names

L-735,524[50]

MK-639[51]

IDV[52]

Indinavir sulfate[53]

Further Reading

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Manufacturer Information

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One Merck Dr
P.O. Box 100
Whitehouse Station, NJ 08889-0100
(800) 609-4618

Crixivan
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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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